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(54) Title: USE OF ROSUVASTATIN (ZD-4522) IN THE TREATMENT OF HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

(57) Abstract: The invention provides a method for the treatment of heterozygous familial hypercholesterolemia by administering the compound (E)-7-[4-(4-fluorphenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof.

USE OF ROSUVASTATIN (ZD-4522) IN THE TREATMENT OF HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

The present invention relates to a new use of a statin drug in the treatment of severe heterozygous familial hypercholesterolemia (HeFH)and in particular patients with baseline LDL-C >220mg/dL.

There is now a large body of evidence obtained from clinical trials demonstrating that pharmacological agents (particularly the statins) that reduce low density lipoprotein-cholesterol LDL-C levels also decrease Chronic Heart Disease (CHD) risk (Lipid Research Clinics Program 1984, Gould et al 1998). Taken together, the trials published to date support the concept that lowering LDL-C levels should be the principal goal of lipid altering therapy (Ansell et al 1999), and that the reduction in coronary risk that occurs during treatment with statins is directly related to these agents' LDL-C lowering effects (Gould et al 1998, Pedersen et al 1998).

Primary hyperlipidemia is a term used to describe a defect in lipoprotein metabolism. The lipoproteins commonly affected are LDL-C, which transports mainly cholesterol, and VLDL-C, which transports mainly TG. Most subjects with hyperlipidemia have a defect in LDL metabolism, characterised by raised cholesterol, LDL-C, levels, with or without raised triglyceride levels; such subjects are termed hypercholesterolemic (Fredrickson Type II). Familial hypercholesterolemia (FH) is caused by any one of a number of genetically-determined defects in the LDL receptor, which is important for the entry of cholesterol into cells. The condition is characterised by a reduced number of functional LDL receptors, and is therefore associated with raised serum LDL-C levels due to an increase in LDL. In its heterozygous form (HeFH) it is one of the commonest genetic diseases, with a frequency of about 1 in 500 in the United Kingdom (US), the United States (US), and Japan (Myant 1981, Mabuchi et al 1979).

LDL and VLDL are known to be atherogenic, and thus subjects with hypercholesterolemia are at increased risk of developing atherosclerosis, a disease process that results in widespread clinical manifestations, including coronary heart disease (CHD), cerebrovascular disease (CVD) and peripheral vascular disease (PVD). In subjects with HeFH, the clinical manifestations of heart disease can occur as early as the mid-twenties. Many subjects with hypercholesterolemia die each year as a result, and many have a reduced quality of life; inevitably, this places very heavy demands on health service resources.

One important goal of therapy in these subjects is to reduce blood cholesterol levels, since this may reduce the progression of the disease and may even induce regression (Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults 1993).

Quoting the % of subjects brought within relevant guidelines (NCEP, EAS) targets for LDL-C levels is a useful way of expressing the efficacy of lipid-regulating agents, and is becoming more commonplace in the literature. The guidelines of the National Cholesterol Education Program (NCEP) and European Atherosclerosis Society (EAS) are well recognised and have been accepted internationally.

Therapies available to treat HeFH include resins, such as cholestyramine and colestipol. Resins reduce LDL-C levels by sequestering bile acids (essential for the absorption of dietary lipid) from the gut and preventing their reabsorption; however, their use is limited by unpalatability and poor subject compliance. Fibrates, such as fenofibrate and gemfibrozil, have a complex mechanism of action on LDL-C, and appear to be of more use in reducing blood TG levels than cholesterol levels; these drugs are therefore less useful in subjects with HeFH (who typically do not have significantly elevated triglyceride levels). Fibrate drugs are thought to act through peroxisomal proliferating activator receptor-α (PPAR-α) and affect gene activation at a number of genes involved in atheroma. Patients on fibrate drugs show improved LDL subfraction distribution (reduced VLDL and raised HDL), reduced LDL and reduced triglyceride levels and possible advantages through improving insulin sensitivity. Examples of fibrate drugs include, bezafibrate, ciprofibrate, fenofibrate and gemfibrozol. Nicotinic acid and its derivatives have some benefit, but are limited by prostaglandin-mediated side effects, such as flushing and dizziness.

A breakthrough in treating hypercholesterolemia has come from agents known as statins. These drugs, which include atorvastatin, pravastatin and simvastatin, lower LDL-C levels by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the enzyme involved in the rate-limiting step in cholesterol biosynthesis in the liver. Partial inhibition of hepatic cholesterol metabolism is thought to result in an increase in the number of cellular receptors for LDL-C, leading to an increased removal of LDL-C from the circulation.

Despite the benefits of statin therapy less than optimal therapeutic results are achieved by the use of statins in patients suffering from HeFH. Typically the majority of patients suffering from HeFH are treated with at least a statin and a fibrate or a statin and a bile acid

sequestrant or possibly all these in an aggressive attempt to reduce the patients LDL-C levels within acceptable guideline limits. Myopathy and rhabdomyolysis have been associated with taking a statin in combination with gemfibrozil and niacin (HMG CoA reductase inhibitors, Hunninghake, Current Opinion in Lipidology (19921) 3, 22-28) as they are all substrates for P450 3A4 and may lead to clinicallly significant drug interactions.

Therefore, currently there is no single drug treatment which may be used on its own which consistently brings a significant number of patients suffering from HeFH within NCEP or EAS guidelines

Risk categories and target LDL-C levels in the NCEP and EAS guidelines

Guideline and risk category	Definition of risk	Target LDL-C level
NCEP		
Low-risk	No CHD or PVD and ≤1 risk factor	<4.14 mmol/L (<160 mg/dL)
Medium risk	No CHD or PVD and ≥2 risk factors	<3.36 mmol/L (<130 mg/dL)
High-risk	Clinically evident CHD, PVD or diabetes	≤2.59 mmol/L (≤100 mg/dL)
EAS		
High-risk	CHD, diabetes or a family history of premature CHD or PVD; or assigned based on a logistic regression model	<3.00 mmol/L (<116 mg/dL)
Other risk	Assigned based on a logistic regression model	<3.00 mmol/L (<116 mg/dL)

We have discovered that (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof (hereinafter called ZD4522), the calcium salt of which is shown in Fig. 1 below, is particularly good at treating heterozygous familial

hypercholesterolemia, in particular severe heterozygous familial hypercholesterolemia (HeFH).

We have conducted a Phase III trial designed to assess the efficacy of ZD4522 in subjects with HeFH. The dose-response of ZD4522 was compared with atorvastatin using the percentage change from baseline in LDL-C levels as the primary end-point. Doses of ZD4522 up to 80 mg per day were used. Atorvastatin was chosen as the comparator statin in this trial because it has the best LDL-C lowering activity of the currently marketed statins.

A larger percentage of patients with heterozygous familial hypercholesterolemia are brought within NCEP or EAS guidelines with treatment of ZD4522 alone than with any other therapy, in particular in high risk patients.

ZD4522 is a statin that demonstrates potent *in vitro* and *in vivo* inhibition of HMG-CoA reductase. Early clinical trials have shown that ZD4522 has a beneficial effect on the lipid profile, by reducing LDL-C, total cholesterol (TC) and TG levels. In addition, ZD4522 has been shown to raise high-density lipoprotein cholesterol (HDL-C) levels.

By the use of the term heterozygous familial hypercholesterolemia we mean patients who have been diagnosed with this type of condition such as patients whose genotype has been determined to be indicative of HeFH. Particular HeFH patients who benefit from ZD4522 are those suffering from severe HeFH. By the use of the term "severe HeFH" we mean patients who are high risk category patients, as defined by the NCEP guidelines (as outlined in JAMA 1993; 269:3015-23 which guidelines and charts are incorporated herein by reference), such patients target LDL-C levels being lower, i.e. ≤100mg/dL.

For the purposes of clarity patients who suffer from homozygous familial hypercholesterolemia are excluded from the scope of this invention.

Therefore we present as a first feature of the invention a method for treating heterozygous familial hypercholesterolemia in a patient suffering heterozygous familial hypercholesterolemia, comprising administering to the patient ZD4522.

ZD4522 is disclosed in European Patent Application, Publication No. 0521471, and in Bioorganic and Medicinal Chemistry, (1997), 5(2), 437-444 as an inhibitor of 3-hydroxy-3-methylglutaryl CoA reductase (HMG-CoA reductase). Preferably the calcium salt is used as illustrated in Figure 1. Preferably the ZD4522 is used at a dose of 5 to 80 mg per day, in particular 40 to 80mg per day.

The pharmaceutical compositions of the present invention may be administered in a standard manner for example by oral or parenteral administration, using conventional systemic dosage forms, such as a tablets, capsules, pills, powders, aqueous or oily solutions or suspensions, emulsions, sterile injectable aqueous or oily solutions or suspensions. These dosage forms will include the necessary carrier material, excipient, lubricant, buffer, bulking agent, anti-oxidant, dispersant or the like. In particular, compositions for oral administration are preferred, for example as disclosed in International Patent Application, Publication No. WO 01/54668.

The dose of ZD4522 which can be administered in accordance with the present invention depends on several factors, for example the age, weight and the severity of the condition under treatment, as well as the route of administration, dosage form and regimen and the desired result. In the treatment of severe heterozygous familial hypercholesterolemia the maximum lipid lowering effect is desired and therefore a maximum dose of at least 40mg a day is recommended, preferably 80 mg a day.

A unit dosage formulation such as a tablet or capsule will usually contain, for example, from 1 mg to 100 mg of ZD4522. Preferably a unit dose formulation will contain 5 to 80 mg ZD4522.

A clinical protocol testing the effectiveness of ZD4522 in heterozygous familial hypercholesterolemia and results is set out below

A 24-Week, Randomised, Double-blind, Multicentre, Multinational Trial to Evaluate the Efficacy and Safety of ZD4522 and Atorvastatin in the Treatment of Subjects with Heterozygous Familial Hypercholesterolemia

OBJECTIVES

The primary objective was to compare the efficacy of ZD4522 (titrated to 80 mg) with that of atorvastatin (titrated to 80 mg) in reducing low-density lipoprotein cholesterol (LDL-C) levels in subjects with heterozygous familial hypercholesterolemia (HeFH) after 18 weeks of treatment.

The secondary objectives were to compare the efficacy of ZD4522 with that of atorvastatin in relation to the following: reducing LDL-C levels after 2, 6, and 12 weeks of treatment; in modifying other lipids and lipoprotein fractions after 2, 6, 12, and 18 weeks of

treatment; in reducing LDL-C levels to within relevant national and international guidelines after 6, 12, and 18 weeks of treatment; in modifying the inflammatory marker C-reactive protein (CRP) after 18 weeks of treatment. A further secondary objective was to determine the safety of ZD4522.

METHODS

Design: A 24-week, randomised, double-blind, 2-group, parallel-group, forced-titration, multicentre, multinational trial. After a 6-week dietary lead-in period, subjects were randomised to treatment with either ZD4522 20 mg, or atorvastatin 20 mg for 6 weeks. Following this initial treatment period, all subjects with an LDL-C level >1.3 mmol/L (50 mg/dL) were force-titrated at 6-week intervals as follows: from ZD4522 20 to 40 to 80 mg, and from atorvastatin 20 to 40 to 80 mg. The maximum titrated dose of either treatment after 18 weeks was 80 mg.

Population: A total of 265 (200 in the ZD4522 group, 65 in the atorvastatin group) randomised to and evaluable subjects with documented heterozygous FH, derived from approximately 1240 recruited subjects, were required to enable 80% power in detecting a 6% difference between groups in the percentage change from baseline in LDL-C levels.

Key inclusion criteria: Men or women aged ≥18 years with heterozygous FH; discontinuation of all cholesterol-lowering drugs and dietary supplements; fasting LDL-C levels between 5.69 and <12.93 mmol/L (220 and <500 mg/dL); fasting triglyceride (TG) levels ≤4.52 mmol/L (400 mg/dL); an Eating Pattern Assessment Tool (EPAT) score of ≤28 to demonstrate dietary compliance.

Key exclusion criteria: Various concomitant illnesses, including active liver disease or hepatic dysfunction (defined by an alanine aminotransferase [ALT], aspartate aminotransferase [AST] or bilirubin concentration ≥1.5 x the upper limit of normal [ULN]), active arterial disease, history of malignancy (unless basal or squamous cell skin carcinoma), uncontrolled hypertension, and uncontrolled hypothyroidism; serum creatine kinase (CK) concentration >3 x ULN; usage of concomitant medications known to affect the lipid profile or present a potential safety concern (for example, through drug interaction).

Dosage: Subjects took oral doses of trial treatment once daily, approximately 3 hours after the evening meal. Doses of treatments were as follows: ZD4522 20, 40, and 80 mg, atorvastatin 20, 40, and 80 mg. Subjects had their doses titrated up at 6-week intervals in a

sequential manner, if appropriate.

Key assessments:

Efficacy: Fasting LDL-C, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and TG were assessed at Weeks 0, 2, 6, 12, and 18; fasting apolipoprotein (ApoB) and apolipoprotein A-I (ApoA-I) were assessed at Weeks 0 and 18; C-reactive protein (CRP) was assessed at Weeks 0 and 18. Dietary compliance throughout the trial was assessed and evaluated.

The primary end-point was the percentage change from baseline to Week 18 in LDL-C levels, and was analysed using analysis of variance (ANOVA) on last observations carried forward (LOCF) from an intention-to-treat (ITT) population; the initial ANOVA model included terms for treatment, centre, and centre-by-treatment interaction. Additional analyses using observed data from ITT and per-protocol (PP) populations were used to confirm the robustness of the main ITT analysis.

Percentage changes from baseline in the other lipids and lipoproteins were secondary end-points of the trial and were analysed using ANOVA. The other secondary end-points of the percentage of subjects in the ITT population who achieved targets for LDL-C levels specified by the National Cholesterol Education Program (NCEP) or the European Atherosclerosis Society (EAS), and the percentage change from baseline in the inflammatory marker CRP, were summarised only.

Subgroup and exploratory analyses were performed on LDL-C and HDL-C data, based on pre-defined demographic groupings.

Safety: Standard safety assessments included adverse event reports, clinical laboratory data (hepatic biochemistry, CK, renal biochemistry, haematology, urinalysis), vital signs, electrocardiograms (ECGs) and physical examination.

RESULTS

Demography: A total of 999 subjects were recruited from 58 centres, and of these, 623 subjects from 57 centres (the one subject in Centre 0254 was not randomised) were eligible for randomisation after the dietary lead-in period. A total of 435 subjects were given ZD4522 20/40/80 mg and 187 subjects were given atorvastatin 20/40/80 mg; one subject who was randomised to the ZD4522 20/40/80 mg treatment group did not take study medication

and was excluded from both ITT and safety populations. Though the number of subjects recruited was lower than the projected number of 1240, the number of screen failures/withdrawals during the dietary lead-in period was approximately half the anticipated failure rate of 60%. As all subjects recruited who had satisfied randomisation criteria were allowed the opportunity to complete the trial and both treatment groups were consequently over-recruited by approximately 100 subjects each. Demographic characteristics were generally well balanced among the treatment groups. The majority of subjects were Caucasians between 18 and 65 years of age, with a mean Body Mass Index (BMI) of 27.13 kg/m2. There were 376 screen failures/withdrawals during the dietary lead-in period, of whom the majority (88%) were screen failures, defined as the failure to meet inclusion/exclusion. Of the 623 subjects randomised to treatment, 34 withdrew; adverse events were the most common reason for withdrawal (71% of subjects withdrawing during the randomisation period). There were 622 subjects in the safety population and the same 622 subjects included the ITT population; there were 514 subjects in the PP population. A total of 589 subjects successfully completed the trial.

Efficacy: A summary of the key efficacy findings is presented in Table I.

Table I Summary of key efficacy findings (LOCF on ITT population)

Efficacy end-point	ZD4522 20/40/80 mg[a]	Atorvastatin 20/40/80 mg[a]
Lsmean of percentage change from baseline to Week 18 in lipids and lipid ratios		
LDL-C	-57.88[b]	-50.41[b]
TC	-46.35[b]	-42.13[b]
HDL-C	12.36[b]	2.91[b]
TG	-27.82[ns]	-31.60[ns]
LDL-C/HDL-C	-61.69[b]	-51.16[b]
TC/HDL-C	-51.44[b]	-43.17[b]
Non-HDL-C/HDL-C	-59.40[b]	-49.86[b]

ApoB	-50.21[b]	-44.44[b]
ApoA-I	5.86[b]	-2.33[b]
ApoB/ApoA-I	-52.03[b]	-42.46[b]
Percentage subjects reaching NCEP or EAS targets for LDL-C levels at Week 18		
NCEP, overall	60.5	46.0
NCEP, high-risk	23.9	3.2
EAS, overall	47.4	24.1
EAS, high-risk	47.5	24.2
Percentage change from baseline to Week 18 in inflammatory marker (Observed data)		
CRP	25.21	31.28

[a] Although force-titrations were scheduled to take place at 6-week intervals, any subject whose most recently recorded LDL-C level was ≤1.3 mmol/L (50 mg/dl) remained on their current dose of trial medication and did not proceed with the next scheduled dose-titration step.

[b] $p<0.001$, [ns] = not significant versus atorvastatin 20/40/80 mg ($p=0.052$).

Statistical analysis was not performed for NCEP and EAS targets.

lsmean = Least squares mean.

In the primary efficacy analysis (LOCF data from the ITT), ZD4522 20/40/80 mg resulted in a significantly ($p<0.001$) greater % reduction in LDL-C levels than did atorvastatin 20/40/80 mg at 18 weeks. The difference between treatments was >6%, the difference on which the trial was powered, and was therefore considered to be clinically relevant (mean % reduction in LDL-C was 57.88% in the ZD4522 20/40/80 mg group and 50.41% in the atorvastatin 20/40/80 mg group). ZD4522 resulted in significantly ($p<0.001$) and clinically greater % reduction in LDL-C at Week 2, 6 and 12. ZD4522 20/40/80 mg also resulted in significantly ($p<0.001$) greater % reductions in TC and significantly ($p\leq0.003$) greater % increase in HDL-C than did atorvastatin 20/40/80 mg at all time points (observed data for Week 2, 6 and 12; observed and LOCF for Week 18). Both ZD4522 20/40/80 mg and atorvastatin 20/40/80 mg reduced TG levels at all time point, but the % reductions were similar in both treatment groups and the differences were not significantly different ($p>0.050$

at 2, 6 and 12 weeks for observed data and 18 weeks for LOCF). ZD4522 20/40/80 mg resulted in significantly ($p<0.001$) greater decreases in ApoB and increases in ApoA-I than did atorvastatin 20/40/80 mg at Week 18 (LOCF). In addition, ZD4522 20/40/80 mg resulted in significantly ($p<0.001$) greater reductions in the LDL-C/HDL-C, TC/HDL-C and non-HDL-C/HDL-C ratios at all time points.

The same finding was true for the ApoB/ApoA-I ratio at Week 18 (LOCF). A greater percentage of subjects in the ZD4522 20/40/80 mg group achieved NCEP and EAS target levels than did those in the atorvastatin 20/40/80 mg group, with the greatest difference between treatments observed for the NCEP high-risk group. Analysis of % change in CRP showed no apparent treatment-related differences; however, data were extremely variable. Results from the PP population generally supported these results. Exploratory and subgroup analyses of % LDL-C reduction from baseline showed significant effects for the following variables: age, baseline HDL-C and baseline TG. Treatment effect was also a significant variable for the baseline TG.

OVERALL CONCLUSIONS

ZD4522 was significantly more effective than atorvastatin in improving the atherogenic lipid profile (LDL-C, HDL-C and TC); ZD4522 was also clinically superior to atorvastatin with respect to effect on LDL-C levels, the primary lipid of interest. ZD4522 resulted in more subjects achieving guideline targets for LDL-C than did atorvastatin, particularly with those at high-risk of cardiovascular disease. ZD4522 had a satisfactory safety profile, which was comparable to atorvastatin.

Primary Endpoint

The main efficacy analyses were based on the ITT (LOCF at 18 weeks); PP and 18 week observed data analyses support use of ITT LOCF analyses.

- ZD4522 reduced LDL-C statistically and clinically significantly more than did atorvastatin at 18 weeks.

Secondary Endpoints

- ZD4522 reduced LDL-C statistically and clinically significantly more than did atorvastatin at 2, 6 and 12 weeks.

- ZD4522 reduced TC statistically significantly more than did atorvastatin at 2, 6, 12 and 18 weeks.
- ZD4522 increased HDL-C statistically significantly more than did atorvastatin at 2, 6, 12 and 18 weeks.
- ZD4522 and atorvastatin demonstrated similar efficacy in reducing TG at all time points.
- ZD4522 reduced Apo B and increased Apo A-I statistically significantly more than did atorvastatin at 18 weeks.
- ZD4522 reduced all four ratios statistically significantly more than did atorvastatin at all time points assessed (LDL-C/HDL-C, TC/HDL-C, non-LDL-C/HDL-C at 6, 12 and 18 weeks and Apo B/Apo A-I at 18 weeks).
- ZD4522 brought a greater proportion of patients within NCEP and EAS guideline targets for LDL-C than did atorvastatin at all time points. This was particularly apparent in the high-risk category patients and was more marked as treatment progressed.
- CRP data were highly variable and there were no apparent treatment-related differences.
- The overall incidence of AEs in the two treatment groups (including treatment-related AEs, AEs leading to withdrawals and SAEs) was similar (61.8% and 65.8% for ZD4522 and atorvastatin, respectively). Overall, there were no treatment-related trends and there were no trends towards increasing incidence with increasing dose.
- There were no clinically significant elevations (≥10xULN) in CK on either treatment. The incidence of clinically significant elevations in ALT (≥3xULN) was 2.3% (10 patients) in the ZD4522 group and 1.1% (2 patients) in the atorvastatin group. The numbers of patients were too small to allow comparative inferences.
- Data on vital signs, ECGs and ophthalmological assessments suggested no obvious differences between treatment groups.

ABBREVIATIONS AND CONVENTIONS

ABBREVIATIONS

Abbreviation	Definition
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (also known as SGPT, serum glutamic pyruvate transaminase)
ANOVA	Analysis of variance
ApoB	Apolipoprotein B
ApoA-I	Apolipoprotein A-I
AST	Aspartate aminotransferase (also known as SGOT, serum oxaloacetic pyruvate transaminase)
BMI	Body mass index
CHD	Coronary heart disease
EAS	European Atherosclerosis Society
FH	Familial hypercholesterolaemia
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HMG-CoA	3-Hydroxy-3-methylglutaryl coenzyme A
ITT	Intention-to-treat
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LOCF	Last observation carried forward
NCEP	National Cholesterol Education Program
PP	Per protocol
PVD	Peripheral vascular disease

Abbreviation	Definition
TC	Total cholesterol
TG	Triglyceride
ULN	Upper limit of normal
VLDL	Very-low-density lipoprotein

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Example 1

Capsule	mg
ZD4522	5.0
Lactose	42.5
Corn starch	20.0
Microcrystalline cellulose	32.0
Pregelatinised starch	3.3

Hydrotalcite	1.1
Magnesium stearate	1.1

Capsules containing 1, 2.5 or 10mg of the ZD4522 may be obtained similarly using more or less lactose as appropriate., to achieve a fill weight of 105mg.

Example 2

Tablet	mg
ZD4522	10
Povidone	10
Mannitol	187.6
Microcrystalline cellulose	188.0
Tribasic calcium phosphate	80.0
Sodium starch glycollate	12.0
Butylated hydroxytoluene	0.2
Magnesium stearate	6.0

Example 3

ZD4522	20
Povidone	3.73
Mannitol	69.41
Microcrystalline cellulose	70.21
Tribasic calcium phosphate	29.88
Sodium starch glycollate	4.48
Butylated hydroxytoluene	0.05
Magnesium stearate	2.0

Tablets containing 40 mg of the ZD4522 can be obtained by doubling the quantities given in Example 3.

Claims

1. A method for treating heterozygous familial hypercholesterolemia in a patient suffering heterozygous familial hypercholesterolemia, comprising administering to the patient (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof.

2. A method as claimed in claim 1 wherein the patient is suffering from severe heterozygous familial hypercholesterolemia.

3. A method as claimed in claim 1 wherein the patient also suffers one or more of the following conditions coronary heart disease, peripheral vascular disease and diabetes.

4. A method as claimed in claim 1 or claim 3 wherein the target LDL-C level for the patient suffering heterozygous familial hypercholesterolemia which is to be achieved by administering to the patient (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof is less than or equal to ≤100 mg/dL.

5. A method as claimed in claim 4 wherein the calcium salt of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid is administered.

6. A method as claimed in claim 5 wherein 40 to 80 mg of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid is administered once a day to the patient in the form of the calcium salt.

7. A method as claimed in claim 5 wherein 80mg of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid is administered once a day to the patient in the form of the calcium salt.

8. A method for reducing LDL-C, raising HDL-C, reducing Apo B and raising Apo A-1 in a patient suffering from heterozygous familial hypercholesterolemia comprising administering to the subject (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof.

9. A method as claimed in claim 1 wherein the patient has a fasting LDL-C level between 5.69 and <12.93 mmol/L.

10. A method as claimed in claim 9 wherein the patient has a fasting triglyceride level less than or equal to 4.52 mmol/L.

11. The use of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of a patient suffering from heterozygous familial hypercholesterolemia.

12. The use as claimed in claim 11 wherein the patient is suffering from severe heterozygous familial hypercholesterolemia.

13. The use as claimed in claim 11 wherein the patient also suffers one or more of the following conditions coronary heart disease, peripheral vascular disease and diabetes.

14. The use as claimed in claim 11 or claim 13 wherein the target LDL-C level for the patient suffering heterozygous familial hypercholesterolemia which is to be achieved by administering to the patient (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof is less than or equal to ≤100 mg/dL.

15. The use as claimed in any of claims 11 to 14 wherein the calcium salt of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid is used.

16. The use as claimed in claim 15 wherein 40 to 80mg of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid is administered once a day to the patient in the form of the calcium salt.

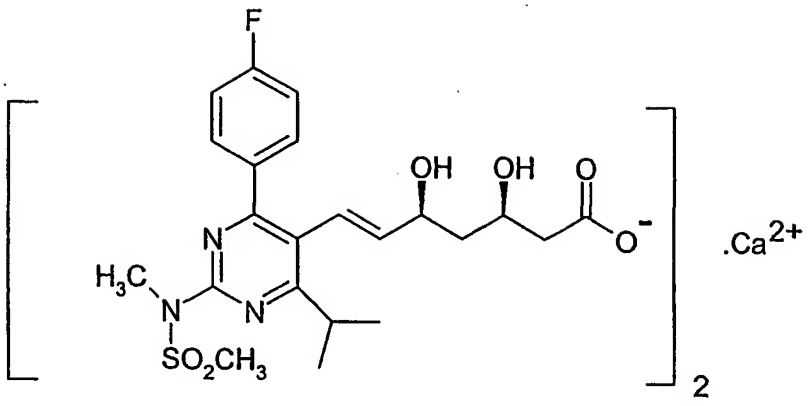
17. The use as claimed in claim 16 wherein 80mg of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid is administered once a day to the patient in the form of the calcium salt.

18. The use of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in reducing LDL-C, raising HDL-C, reducing Apo B and raising Apo A-1 in a patient suffering from heterozygous familial hypercholesterolemia.

19. The use as claimed in claim 18 wherein the patient has a fasting LDL-C level between 5.69 and <12.93 mmol/L.

20. The use as claimed in claim 19 wherein the patient has a fasting triglyceride level less than or equal to 4.52 mmol/L

Figure 1.



ZD4522

INTERNATIONAL SEARCH REPORT

onal Application No
PCT/GB 01/05041

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/505 A61P3/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data, MEDLINE, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KOIZUMI JUNJI ET AL: "Clinical Efficacy of Fluvastatin in the Long-Term Treatment of Familial Hypercholesterolemia." AMERICAN JOURNAL OF CARDIOLOGY, vol. 76, no. 2, 1995, pages 47A-50A, XP001053598 ISSN: 0002-9149 page 47A, left-hand column, paragraph 1 -right-hand column, paragraph 2 page 48A, right-hand column, paragraph 6 -page 49A, left-hand column, paragraph 5 --- -/--	1-20

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 March 2002	18/04/2002

Name and mailing address of the ISA	Authorized officer
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If ional Application No
PCT/GB 01/05041

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KITATANI M ET AL: "A 4-YEAR trial of simvastatin in the treatment of patients with heterozigous OF FAMILIAL HYPERCHOLESTEROLAEMIA" CURRENT THERAPEUTIC RESEARCH, vol. 57, no. 1, 1996, pages 62-71, XP001064046 ISSN: 0032-5473 abstract page 62, paragraph 1 -page 63, paragraph 4 page 64, paragraphs 3,4 page 66, paragraph 2 -page 68, paragraph 2 ---	1-20
Y	KOIZUMI JUNJI ET AL: "Reduction of lipoprotein (a) by LDL-apheresis using a dextran sulfate cellulose column in patients with familial hypercholesterolemia." ATHEROSCLEROSIS, vol. 100, no. 1, 1993, pages 65-74, XP001053599 ISSN: 0021-9150 abstract page 66, right-hand column, paragraph 2 table 3 figure on page 71 page 72, left-hand column, paragraph 3 -right-hand column, paragraph 2 ---	1-20
Y	STEIN EVAN A ET AL: "Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia: A randomized controlled trial." JAMA (JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION), vol. 281, no. 2, 13 January 1999 (1999-01-13), pages 137-144, XP001053593 ISSN: 0098-7484 abstract page 138, column C, paragraph 1 page 140, left-hand column, paragraph 2 -right-hand column, paragraph 2 table 2 --- -/--	1-20

INTERNATIONAL SEARCH REPORT

nal Application No
PCT/GB 01/05041

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WATANABE M ET AL: "SYNTHESIS AND BIOLOGICAL ANTIVITY OF METHANESULFONAMIDE PYRIMIDINE-AND N-METHANESULFONYL PYRROLE-SUBSTITUTED 3,5-DIHYDROXY-6-HEPTENOATES, A NOVEL SERIES OF HMG-COA REDUCTASE INHIBITORS" BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER SCIENCE LTD, GB, vol. 5, no. 2, 1997, pages 437-444, XP000882043 ISSN: 0968-0896 cited in the application page 437, left-hand column, paragraph 1 -right-hand column, paragraph 2 figure 1 ---	1-20
Y	EP 0 521 471 A (SHIONOGI & CO) 7 January 1993 (1993-01-07) cited in the application page 2, line 1-22 Compound of formula I a-1 and its corresponding calcium salt. page 13, line 19 -page 14, line 22 ---	1-20
Y	OLSSON A ET AL: "ZD4522: A new HMG-CoA reductase inhibitor-causes rapid and profound reductions in plasma LDL-C levels in patients with primary hypercholesterolaemia." EUROPEAN HEART JOURNAL, vol. 21, no. Abstract Supplement, August 2000 (2000-08), page 156 XP001053584 XXII Congress of the European Society of Cardiology;Amsterdam, Netherlands; August 26-30, 2000 ISSN: 0195-668X abstract ---	1-20
Y	PEARS J S ET AL: "Dose-ranging study of the HMG-CoA reductase inhibitor ZD4522 in patients with primary hypercholesterolemia." CANADIAN JOURNAL OF CARDIOLOGY, vol. 16, no. Supplement F, September 2000 (2000-09), page 196F XP001053592 53rd Annual Meeting of the Canadian Cardiovascular Society;Vancouver, British Columbia, Canada; October 20-November 01, 2000 ISSN: 0828-282X abstract --- -/--	1-20

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/05041

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	STEIN EVAN A ET AL: "ZD4522 (rosuvastatin) compared with diet and maximal lipid therapy in patients with heterozygous familial hypercholesterolemia." JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, vol. 37, no. 2 Supplement A, February 2001 (2001-02), page 291A XP001053700 50th Annual Scientific Session of the American College of Cardiology;Orlando, Florida, USA; March 18-21, 2001 ISSN: 0735-1097 abstract	1-20
P,X	STEIN EVAN ET AL: "ZD4522 is superior to atorvastatin in the treatment of patients with heterozygous familial hypercholesterolemia." JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, vol. 37, no. 2 Supplement A, February 2001 (2001-02), page 292A XP002191237 50th Annual Scientific Session of the American College of Cardiology;Orlando, Florida, USA; March 18-21, 2001 ISSN: 0735-1097 abstract	1-20
P,X	OLSSON ANDERS G: "A new statin: A new standard." CLINICAL CARDIOLOGY, vol. 24, no. 8 Supplement 3, August 2001 (2001-08), pages III-18-III-23, XP001053596 ISSN: 0160-9289 the whole document	1-20

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 8-10 and 18-20 relate to a method for and to the use of a claimed compound in the manufacture of a medicament for use in "reducing LDL-C, raising HDL-C, reducing Apo B and raising Apo A-1". Even if said method is said to be applied to patients suffering from heterozygous familial hypercholesterolemia, the use of terms such as "reducing" and "raising" the parameters listed above, in the present contest is considered to lead to a lack of clarity within the meaning of Article 84 EPC. It does not seem fully possible to determine the actual therapeutic application for which protection might legitimately be sought.
Independent of the above reasoning, the claims 4 and 14 also lack clarity (Article 6 PCT). An attempt is made to define the therapeutic application by reference to a result to be achieved (target LDL-C level less than or equal to 100 mg/dL). Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been restricted to the real and defined disease mentioned in claim 1 and 8 (heterozygous familial hypercholesterolemia) with due regard to the general idea underlying the present invention.

Claims not searched: none.
Claims searched incompletely: 4,8-10,14,18-20.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

.nformation on patent family members

Inal Application No
PCT/GB 01/05041

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		DE	69231530 T2	13-06-2001
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		US	RE37314 E1	07-08-2001
		US	5260440 A	09-11-1993